EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF CYCLOHEXANOL

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California Environmental Protection Agency (Cal/EPA)

CYCLOHEXANOL (CAS No. 108-93-0)

- Molecular formula: $C_6H_{12}O$
- Molecular weight: 100.16
- Used in production of nylon, lacquers, paints, varnishes, degreasers, plastics and plasticizers, soaps and detergents, textiles, and insecticides
- Exposure may be oral, inhalation, or dermal

PHARMACOKINETICS OF CYCLOHEXANOL

- Absorbed by oral, inhalation, or dermal routes
- May increase skin penetration of other substances
- Primarily oxidized by hepatic NAD-dependent alcohol dehydrogenase (ADH)
- Excreted as glucuronide or sulfate conjugate

ACUTE LD_{50} OF CYCLOHEXANOL

	Mouse	Rat	Rabbit
Oral	-	>1,400-2,060 mg/kg	>2,200-2,600 mg/kg
Dermal	-	-	>12,400-22,700 mg/kg
Inhalation	-	>6,500 mg/m^3	-
iv	270 mg/kg	-	-
sc	1,420-2,480 mg/kg	-	-
ip	760 mg/kg	-	-

DEVELOPMENTAL TOXICITY OF CYCLOHEXANOL

Gondry, E., 1972 – Oral reproduction study in mice

1,200 mg/kg-day, continuous exposure

Increased pup mortality at PND 21

12% in controls (both strains)

43% in NMRI mice

14% in TB mice

53.5% in 2d generation TB

Decreased weight of female pups

SUPPLEMENTAL INFORMATION ON THE DEVELOPMENTAL TOXICITY OF CYCLOHEXANOL

Groth et al., 1993 – Cultured zebrafish embryos

1-30 mMol/L

Altered morphology

Generalized developmental retardation

FEMALE REPRODUCTIVE TOXICITY OF CYCLOHEXANOL

Gondry, E., 1972 – Oral reproduction study in mice

1,200 mg/kg-day

Female mice treated during mating, gestation, and lactation, but no data presented on female reproduction

MALE REPRODUCTIVE TOXICITY OF CYCLOHEXANOL (1)

Tyagi et al. 1979 – 15 mg/kg-day by s.c.

21 days to gerbils, 37 days to rats

No effect on body or adrenal weights

Decreased relative weights of reproductive organs

Histological alterations

Biochemical changes

MALE REPRODUCTIVE TOXICITY OF CYCLOHEXANOL (2)

Dixit et al., 1980 – 25 mg/kg-day by oral route

- 40 days to rabbits
  - No effect on body or adrenal weights
  - Decreased relative weights of reproductive organs
  - Histological alterations
  - Biochemical changes
  - Effects largely reversed after 70 days

MALE REPRODUCTIVE TOXICITY OF CYCLOHEXANOL (3)

Lake et al., 1982 – 455 mg/kg-day by gavage

30-day old rats treated for 7 days

Increased relative liver weights

Increased hepatic enzyme activities and cytochrome P450

No effect on relative kidney or testes weights

SUMMARY (1)

Developmental toxicity

No data in humans

Postnatal data in mice, supplementary data in fish

Female reproductive toxicity

No data in humans

Indirect data in mice

SUMMARY (2)

Male reproductive toxicity

S.c. route in gerbils and rats (15 mg/kg-day, 21-37 days), and

Oral route in rabbits (25 mg/kg-day, 40 days)

> Effects on weight, histology, and biochemistry of reproductive organs

Oral route in rats (455 mg/kg-day, 7 days)

> No effects noted on male reproductive organs